The reemergence of pertussis and infant deaths: is it time to immunize pregnant women?

"A pilot project ... to immunize postpartum women before they left the hospital was successful but was very resource-intensive to implement."

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Pertussis vaccines have been in widespread use for more than 70 years in developed nations. Through the initial use of whole-cell pertussis vaccines and later acellular pertussis vaccines in an infant series, a reinforcing dose in the second year of life and a preschool booster, pertussis has been substantially controlled in children aged 6 months to 8–10 years [1]. In the last two decades, the epidemiology of pertussis has noticeably changed, with a shift of cases to adolescents and adults and children too young to have completed their infant immunization series [2–4]. To address the increase in cases in adolescents and adults, a booster dose is recommended for all adolescents, using an adult-formulation tetanus and diphtheria toxoid and acellular pertussis vaccine (DTaP) [5,6]. For adults, substitution of a single dose of Tdap for the next decennial dose of adult-formulation tetanus and diphtheria toxoid vaccine (Td) is recommended by several expert advisory bodies [5,7]. Whether additional doses of Tdap will be required throughout adulthood depends on the duration of persistence of antibody in adults post-Tdap vaccination [8–10] and the results of epidemiological studies that examine the duration of protection.

Much of the morbidity and virtually all of the mortality related to pertussis occurs in infants [11]. In the USA and Canada, infant deaths from pertussis usually occur in infants too young to have completed their three-dose primary series or in infants whose immunizations were delayed [12,13]. It is hoped that immunization of adolescents and adults might contribute to protection of young infants through herd immunity but no such effect has been observed yet, perhaps owing to low rates of immunization amongst these older age groups [14]. Recent outbreaks of pertussis in Costa Rica [15], California (USA) [16] and Saskatchewan (Canada) [101] have been associated with increased reports of infant deaths. Targeted immunization of adults in close contact with newborns (the so-called cocoon strategy) has been recommended in a number of jurisdictions and has met with mixed success. In France and Germany, there has been little compliance with the recommendation [17]. In Costa Rica, where the strategy was more aggressively implemented, infant deaths from pertussis did decrease but it is unclear whether this was the effect of the strategy of postpartum Tdap immunization or the natural waning of the outbreak [15]. A pilot project in Houston (TX, USA) to immunize postpartum women before they left the hospital was successful but was very resource-intensive to implement [18].

Another strategy being explored to improve the protection of young infants is adding a neonatal dose of pertussis vaccine; however, clinical trials have shown mixed results. In one study, infants given pediatric-formulation diphtheria and tetanus toxoid and acellular pertussis vaccine (DTaP) at birth, 2, 4 and 6 months had lower antibody levels at 7 months than infants routinely immunized at 2, 4 and 6 months [19]. However, other studies that used acellular pertussis vaccine (aP) at birth and 1 month of age rather than DTaP found increased antibody titers against pertussis antigens at 2 and 8 months of age but lower levels of antibodies against *Haemophilus influenzae* type B and hepatitis B [20,21], although these infants boosted normally in the second year of life [22]. Additional studies are currently underway to further explore the benefits of neonatal immunization.

Keywords
■ pertussis ■ pertussis vaccine ■ pregnancy

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Even if successfully implemented, both neonatal immunization and the cocoon strategy still leave neonates unprotected in the vulnerable first months of life. Infants receiving a neonatal dose don't show measurable levels of antibody until after their second dose at 2 months of age (clearly sooner than without the neonatal dose) but they still remain susceptible throughout the neonatal period. Likewise, women immunized postpartum begin to demonstrate an antibody response 7 days postvaccination but don't achieve peak levels until 10–14 days after their dose [Halperin BA *et al.*, Unpublished Data], thus not providing the cocooning effect for the first two postpartum weeks. In the USA, 58% of the 91 fatal cases between 1999 and 2004 occurred in the first 2 months of life [23]; it is likely that many of these cases would not have been prevented by either neonatal immunization or the cocoon strategy.

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Immunization during pregnancy is a well-established method for providing protection for both the mother and newborn infant. Tetanus immunization during pregnancy has been shown to be safe and has contributed to the drastic reduction of cases of neonatal tetanus in the developing world [24]. Immunization against influenza is recommended for all women during pregnancy because of the increased risk of hospitalization and severe disease, which increases during each trimester [25,26]. Recently, it has been demonstrated that newborns of women immunized against influenza during pregnancy have lower rates of disease and hospitalization during the first several months of age [27,28]. Tdap vaccine has not been studied during pregnancy but is classified by the US FDA as a pregnancy category C drug, which indicates that animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the vaccine in pregnant women despite potential risks. In Canada, the National Advisory Committee on Immunization recommends that the use of Tdap during pregnancy be assessed on a case-by-case basis, weighing the potential benefits and risk [5]. Similarly, the Advisory Committee on Immunization Practices of the US CDC recommends that Tdap be used when the potential benefits outweigh the potential risks [102]. By contrast, the American Academy of Pediatrics recommends that Tdap be given to all adolescents, regardless of pregnancy status [29]. Indeed, given the safety record of tetanus toxoid during pregnancy, the theoretical risks of Tdap to the pregnant woman or fetus are likely to be negligible. More concerning than the risk of Tdap during pregnancy is whether the high levels of antibodies induced in the mother and actively and passively transferred transplacentally to the fetus will interfere with the infant's response to active routine immunization at 2, 4 and 6 months of age. Although this is a potential risk, increased protection in the neonatal period with a degree of decreased protection between the 6-month dose and the second-year dose may be an acceptable trade off. If antibody levels are lower after the 6-month dose, administering the second-year booster at 12 months of age to boost antibody titers is an option.

At present, two clinical trials of Tdap immunization during the third trimester of pregnancy are underway in Canada [103] and the USA [104]. Both are evaluating the safety and immunogenicity of Tdap in pregnant women and measuring the response to routine DTaP active immunization in the infants. Information from these studies that will inform practice is still many months away, given the need to wait for the infants of the immunized women to complete their own primary immunization series. In the interim, what should be done to protect newborns from pertussis? In view of the relative risks and benefits, it is reasonable to offer Tdap vaccine to pregnant women whose infants will be at substantial risk of exposure to pertussis. In areas where pertussis is not currently being reported, awaiting the data from the ongoing clinical trials makes sense. In jurisdictions that are experiencing widespread pertussis outbreaks, the risk benefit equation favors immunization with Tdap during the third trimester.

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Bibliography

1. Cherry JD: The present and future control of pertussis. *Clin. Infect. Dis.* 51(6), 663–667 (2010).
2. Galanis E, King AS, Varughese P, Halperin SA, on behalf of the IMPACT investigators: Changing epidemiology and emerging risk groups for pertussis. *CMAJ* 174(4), 451–452 (2006).
3. Skowronski DM, De Serres G, MacDonald D *et al.*: The changing age and seasonal profile of pertussis in Canada. *J. Infect. Dis.* 185(10), 1448–1453 (2002).
4. Güriş D, Strebel PM, Bardenheier B *et al*: Changing epidemiology of pertussis in the United States: increasing reported incidence among adolescents and adults, 1990–1996. *Clin. Infect. Dis.* 28(6), 1230–1237 (1999).
5. National Advisory Committee on Immunization (NACI): Statement on the prevention of pertussis in adolescents and adults. *Can. Commun. Dis. Rep.* 29(ACS-5), 1–9 (2003).
6. Centers for Disease Control and Prevention. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* 55(RR3), 1–34 (2006).
7. Centers for Disease Control and Prevention. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* 55(RR17), 1–37 (2006).
8. Bailleux F, Coudeville L, Kolenc-Saban A, Bevilacqua J, Barreto L, André P: Predicted long-term persistence of pertussis antibodies in adolescents after an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine, based on mathematical modeling and 5-year observed data. *Vaccine* 26(31), 3903–3908 (2008).
9. Barreto L, Guasparini R, Meekison W, Noya F, Young L, Mills E: Humoral immunity 5 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. *Vaccine* 25(48), 8172–8179 (2007).
10. Edelman K, He Q, Mäkinen J *et al.*: Immunity to pertussis 5 years after booster immunization during adolescence. *Clin. Infect. Dis.* 44(10), 1271–1277 (2007).
11. Halperin SA, Wang EEL, Law B *et al.*: Epidemiological features of pertussis in hospitalized patients in Canada, 1991–1997, Report of the Immunization Monitoring Program – Active (IMPACT). *Clin. Infect. Dis.* 28(6), 1238–1243 (1999).
12. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV: Trends in pertussis among infants in the United States, 1980–1999. *JAMA* 290(22), 2968–2975 (2003).
13. Mikelova LK, Halperin SA, Scheifele D *et al.*: Predictors of death in infants hospitalized with pertussis: A case-control study of 16 pertussis deaths in Canada. *J. Pediatr.* 143(5), 576–581 (2003).
14. Centers for Disease Control and Prevention. Tetanus and pertussis vaccination coverage among adults aged ≥18 years – United States, 1999 and 2008. *Morbid. Mortal. Wkly Rep.* 59(40), 1302–1306 (2010).
15. Ulloa-Gutierrez R, Avila-Aguero ML: Pertussis in Latin America: current situation and future vaccination challenges. *Expert Rev. Vaccines* 7(10), 1569–1580 (2008).
16. Roehr B: Whooping cough outbreak hits several US states. *BMJ* 24, 341 (2010).
17. Forsyth KD, Wirsing von Konig C-H, Tan T, Caro J, Plotkin S: Prevention of pertussis: Recommendations derived from the second Global Pertussis Initiative roundtable meeting. *Vaccine* 25(14), 2634–2642 (2007).
18. Healy CM, Rench MA, Baker CJ: Implementation of cocooning against pertussis in a high-risk population. *Clin. Infect. Dis.* 52(2), 157–162 (2011).
19. Halasa NB, O'Shea A, Shi JR, LaFleur BJ, Edwards KM: Poor immune responses to a birth dose of diphtheria, tetanus, and acellular pertussis vaccine. *J. Pediatr.* 153(3), 327–332 (2008).
20. Wood N, McIntyre P, Marshall H, Roberton D: Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age. *Pediatr. Infect. Dis. J.* 29(3), 209–215 (2010).
21. Knuf M, Schmitt HJ, Wolter J *et al.*: Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. *J. Pediatr.* 152(5), 655–660 (2008).
22. Knuf M, Schmitt HJ, Jacquet JM *et al.*: Booster vaccination after neonatal priming with acellular pertussis vaccine. *J. Pediatr.* 156(4), 675–678 (2010).
23. Haberling DL, Holman RC, Paddock CD, Murphy TV: Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. *Pediatr. Infect. Dis. J.* 28(3), 194–198 (2009).
24. Demicheli V, Barale A, Rivetti A: Vaccines for women to prevent neonatal tetanus. *Cochrane Database Syst. Rev.* 4, CD002959 (2005).
25. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR: Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am. J. Epidemiol.* 148(11), 1094–1102 (1998).
26. Dodds L, McNeil SA, Fell DB *et al.*: Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 176(4), 463–468 (2007).
27. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M: Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin. Infect. Dis.* 51(12), 1355–1361 (2010).
28. Eick AA, Uyeki TM, Klimov A *et al.*: Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch. Pediatr. Adolesc. Med.* 165(2), 104–111 (2011).
29. American Academy of Pediatrics Commitee on Infectious Diseases. Prevention of pertussis among adolescents: recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. *Pediatrics* 117(3), 965–978 (2006).

Websites

101. Lawrence R: Whooping cough on the rise in Saskatchewan. The Moose Jaw Times Herald 30 Sep 2010 www.mjtimes.sk.ca/News/Local/2010–09–30/article-1809662/Whooping-Cough-on-the-rise-in-Saskatchewan/ (Accessed 29 December 2010)
102. Centers for Disease Control and Prevention. Guidelines for vaccinating pregnant women. 2007 May www.cdc.gov/vaccines/pubs/preg-guide.htm. (Accessed 29 December 2010)
103. Dalhousie University. Pertussis maternal immunization study. ClinicalTrials.gov identifier NCT00553228 www.clinicaltrials.gov/ct2/show/NCT00553228?term=pertussis+and+pregnancy&rank=1 (Accessed 26 January 2011)
104. National Institute of Allergy and Infectious Diseases (NIAID). Pertussis vaccine in healthy pregnant women. ClinicalTrials.gov identifier NCT00707148 www.clinicaltrials.gov/ct2/show/NCT00707148?term=pertussis+and+pregnancy&rank=2 (Accessed 26 January 2011)